(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 September 2004 (02.09.2004)

PCT

(10) International Publication Number
WO 2004/073704 A1

(51) International Patent Classification[7]: A61K 31/166, 31/167, 31/47, A61P 29/02, C07C 235/46

(21) International Application Number: PCT/SE2004/000196

(22) International Filing Date: 16 February 2004 (16.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0300445-4 18 February 2003 (18.02.2003) SE

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:
— *with international search report*

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(54) Title: NEW COMBINATION

(57) Abstract: The invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient which is a $P2X_7$ receptor antagonist, and a second active ingredient which is an inhibitor of proTNFα; convertase enzyme (TACE), for use in the treatment of inflammatory disorders.

NEW COMBINATION

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of inflammatory conditions/disorders, especially rheumatoid arthritis.

Chronic inflammatory disorders such as rheumatoid arthritis are polygenic, highly complex, and involve multiple inflammatory and immune mechanisms. Treatment of these disorders has been largely empirical with a variety of therapeutic agents being used with little understanding of the mechanisms involved. Recent research suggests that two inflammatory mediators, the cytokines IL-1 and TNFalpha (TNFα), may play key roles in the inflammatory process in rheumatoid arthritis.

It would be desirable to develop new pharmaceuticals for use in treating inflammatory conditions/disorders.

In accordance with the present invention, there is therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient which is a $P2X_7$ receptor antagonist, and a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE).

The $P2X_7$ receptor (previously known as P2Z receptor) is a ligand-gated ion channel that is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, is known to lead, amongst other things, to the release of interleukin-1β (IL-1β).

An antagonist of the $P2X_7$ receptor is a compound or other substance that is capable of preventing, whether fully or partially, activation of the $P2X_7$ receptor.

Methods for assaying for $P2X_7$ receptor antagonism are known in the art, for example from WO 01/42194 which describes an assay based on the observation that when the $P2X_7$ receptor is activated using a receptor agonist in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Thus, an increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound or substance on the $P2X_7$ receptor.

In WO 01/42194, the assay is carried out by taking a 96-well flat bottomed microtitre plate and filling the wells with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4}M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5}M benzoylbenzoyl adenosine triphosphate (bbATP, a known $P2X_7$ receptor agonist), and 25 µl of the high potassium buffer solution containing 3×10^{-5}M test compound. The plate is covered with a plastics sheet and incubated at 37 °C for one hour. The plate is then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and pyridoxal 5-phosphate (a $P2X_7$ receptor antagonist) are used separately in the test as controls. From the readings obtained, a pIC_{50} figure is calculated for the test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. A pIC_{50} figure greater than 5.5 is normally indicative of an antagonist.

TACE (also known as ADAM17) which has been isolated and cloned [R.A. Black *et al.* (1997) Nature 385:729-733; M.L. Moss *et al.* (1997) Nature 385:733-736] is a member of the admalysin family of metalloproteins. TACE has been shown to be responsible for the cleavage of pro-TNFα, a 26kDa membrane bound protein to release 17kDa biologically active soluble TNFα [Schlondorff *et al.* (2000) Biochem. J. 347: 131-138]. TACE mRNA is found in most tissues, however TNFα is produced primarily by activated monocytes, macrophages and T lymphocytes involved in the inflammatory/immune process.

An inhibitor of TACE is a compound or other substance that is capable of inhibiting the activity of proTNFα convertase enzyme, whether fully or partially.

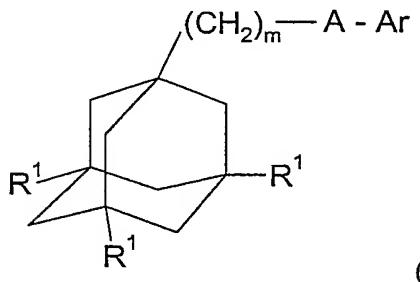
The ability of a compound or substance to inhibit proTNFα convertase enzyme (TACE) may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.-Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 4 hours. Activity is determined by measuring the fluorescence at λex 485nm and λem 538nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

The substrate may be synthesised as follows. The peptidic part of the substrate is assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 are double-coupled. The following side chain protection strategy is employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group is removed by treating the Fmoc-peptidyl-resin in dimethyl formamide (DMF). The amino-peptidyl-resin so obtained is acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161] which has been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF. The dimethoxyfluoresceinyl-peptide is then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and

triethylsilane. The dimethoxyfluoresceinyl-peptide is isolated by evaporation, triturated with diethyl ether and filtered. The isolated peptide is reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product is purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product can be characterised by MALDI-TOF MS and amino acid analysis.

Examples of $P2X_7$ receptor antagonists include the compounds described in WO 00/61569, WO 01/42194, WO 01/44170 and WO 03/041707 , the entire contents of which are incorporated herein by reference.

More specifically, WO 00/61569 discloses a compound of formula



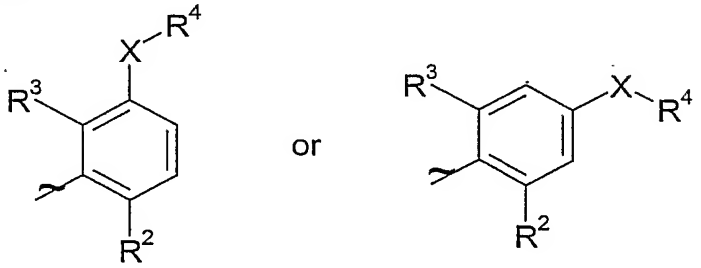
(I)

wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

Ar represents a group



;

X represents a bond, an oxygen atom or a group CO, $(CH_2)_{1-6}$, CH=, $(CH_2)_{1-6}O$, $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, CR'(OH), $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, NR^5, $(CH_2)_{1-6}NR^5$, $NR^5(CH_2)_{1-6}$, $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$, $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$, $NR^5(CH_2)_{2-6}O$,

$NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$, $CONR^5$, NR^5CO, $S(O)_n$, $S(O)_nCH_2$, $CH_2S(O)_n$, SO_2NR^5 or NR^5SO_2;

n is 0, 1 or 2;

R' represents a hydrogen atom or a C_1-C_6 alkyl group;

one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one C_3-C_6 cycloalkyl, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkyloxy optionally substituted by at least one C_3-C_6 cycloalkyl, and (iv) C_3-C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

either R^4 represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$,

or R^4 represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1-C_6 alkyl;

r is 1, 2, 3, 4, 5 or 6;

R^5 represents a hydrogen atom or a C_1-C_6 alkyl or C_3-C_8 cycloalkyl group;

R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

with the provisos that,

(a) when A represents C(O)NH and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(b) when A represents C(O)NH and X represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

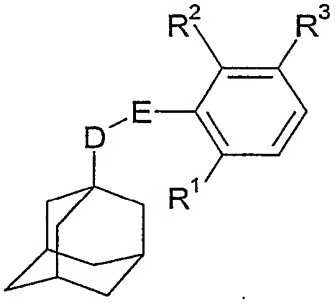
(c) when A represents NHC(O) and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(d) when A represents NHC(O) and X represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2, then R^4 does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A represents NHC(O) and X represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^4 does not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

WO 01/42194 discloses a compound of formula



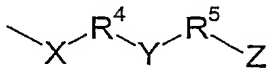
(II)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula



(III);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NR^{11}, SO or SO_2;

Z represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, imidazolyl, 1-methylimidazolyl, $-N(R^{10})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group;

R^6, R^7, R^8, R^9, R^{10}, R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;

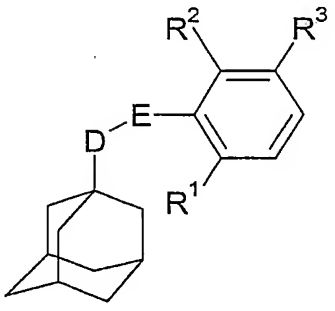
R^{11} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15} and R^{16} each independently represent a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents $-NR^6R^7$ where R^6 represents a hydrogen atom and R^7 represents either a hydrogen atom or a C_1-C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

WO 01/44170 discloses a compound of formula



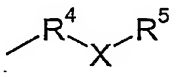
(IV)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent hydrogen, halogen, amino, nitro, C_1-C_6 alkyl or trifluoromethyl, but R^1 and R^2 may not both simultaneously represent hydrogen;

R^3 represents a group of formula

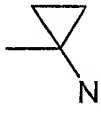


(V);

R^4 represents a C_1-C_6 alkyl group;

X represents an oxygen or sulphur atom or a group NR^{13}, SO or SO_2;

R^5 represents hydrogen, or R^5 represents C_1-C_6 alkyl or C_2-C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)-C_1-C_6-alkylamino, -Y-R^6,



, and

a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1-C_6 alkyl;

Y represents an oxygen or sulphur atom or a group NH, SO or SO_2;

R^6 represents a group -R^7Z where R^7 represents a C_2-C_6 alkyl group and Z represents an -OH, -CO_2H, -NR^8R^9, -C(O)$NR^{10}R^{11}$ or -N(R^{12})C(O)-C_1-C_6 alkyl group, and, in the case where Y represents an oxygen or sulphur atom or a group NH, R^6 additionally represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, -C(O)$NR^{14}R^{15}$, -CH_2OC(O)R^{16}, -CH_2OC(O)OR^{17} or -C(O)OCH_2OR^{18};

R^8, R^9, R^{10}, R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

R^{13} represents hydrogen, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylmethyl, or R^{13} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15}, R^{16}, R^{17} and R^{18} each independently represent a C_1-C_6 alkyl group;

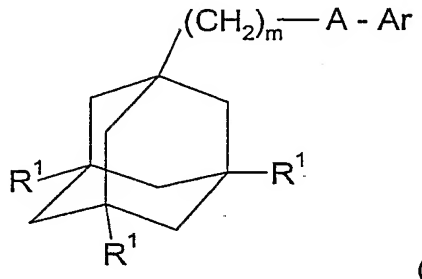
with the proviso that when E is C(O)NH, X is O, NH or N(C_1-C_6 alkyl), then R^5 is other than a hydrogen atom or an unsubstituted C_1-C_6 alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

Preferred compounds of formula (IV) are those wherein R^5 represents an optionally substituted C_1-C_6 alkyl group. A preferred substituent is -Y-R^6.

When R^5 is substituted with a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms, it is preferred that the number of nitrogen atoms in the heteroaromatic ring is not greater than 2.

WO 03/041707 discloses a compound of formula



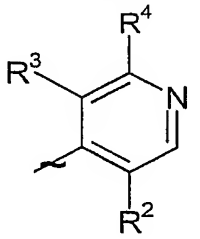
(VI)

wherein m represents 1, 2 or 3;

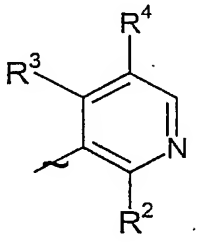
each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

Ar represents a group

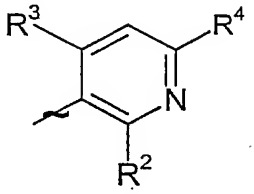


(VII)



(VIII)

or



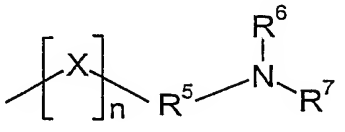
(IX)

;

one of R^2 and R^3 represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkoxy optionally substituted by at least one halogen

atom, and (iv) C_3-C_8 cycloalkyloxy, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

R^4 represents a group



(X);

X represents an oxygen or sulphur atom or a group >N-R^8;

n is 0 or 1;

R^5 represents a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

R^6 and R^7 each independently represent a hydrogen atom, C_1-C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1-C_6 alkoxy, and (di)-C_1-C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3-C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy); and

R^8 represents a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

with the provisos that:

(a) when n is 0, then A is NHC(O), and

(b) when n is 1, X represents oxygen and A is C(O)NH, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl; and

(c) when n is 1, X is oxygen, sulphur or >NH and A is NHC(O), then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl or $-CH_2CH_2OH$;

or a pharmaceutically acceptable salt or solvate thereof.

In an embodiment of the invention, the $P2X_7$ receptor antagonist is

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide hydrochloride,

2-Chloro-5-(piperidin-4-ylsulfinyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-2-chloro-5-(3-{[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl)nicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{[(2*S*)-2-hydroxypropyl]amino}propyl)isonicotinamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

Pharmaceutically acceptable salts include, where applicable, acid addition salts derived from pharmaceutically acceptable inorganic and organic acids such as a chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salt; and salts prepared from pharmaceutically acceptable inorganic and organic bases. Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and bismuth salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, cyclic amines like arginine, betaine, choline and the like.

Examples of pharmaceutically acceptable solvates include hydrates.

Examples of inhibitors of TACE include the compounds described in WO 99/18074, WO 99/65867, US 6225311, WO 00/00465, WO 00/09485, WO 98/38179, WO 02/18326 and WO 02/096426, the entire contents of which are incorporated herein by reference.

In an embodiment of the invention, the TACE inhibitor is

3-Amino-N-hydroxy-α-(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide (also known as DPC-333),

2(S),3(S)-Piperidinedicarboxamide, N3-hydroxy-1-methyl-N2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl],

3-Thiomorpholinecarboxamide, 4-[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy-2, dimethyl (also known as TMI-1),

5-Hexenoic acid, 3-[(hydroxyamino)carbonyl]-2-(2-methylpropyl)-6-phenyl-, 2-(2-methylpropyl)-2-(methylsulfonyl)hydrazide, (2R,3S,5E) (also known as Ro 32-7315),

2-Piperidinecarboxamide, N,5-dihydroxy-1-[[4-(1-naphthalenylmethoxy)phenyl]sulfonyl]-, (2R,5R),

Pentanamide, 3-(formylhydroxyamino)-4-methyl-2-(2-methylpropyl)-N-[(1S,2S)-2-methyl-1-[(2-pyridinylamino)carbonyl]butyl]-, (2R,3S) (also known as GW 3333),

2-Propenamide, N-hydroxy-3-[3-[[(4-methoxyphenyl)sulfonyl](1-methylethyl)amino]phenyl]-3-(3-pyridinyl)-, (2E) (also known as W-3646),

Benzamide, N-(2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl)-4-[(2-methyl-4-quinolinyl)methoxy],

Benzamide, N-[(1-acetyl-4-piperidinyl)(2,5-dioxo-4-imidazolidinyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy], or

2,4-Imidazolidinedione, 5-methyl-5-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]methyl].

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, and a preparation of a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE), for simultaneous, sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, a preparation of a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE), and instructions for the

simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

It has been found that the choice of active ingredients according to the invention is advantageous because it results in a beneficial anti-inflammatory effect and, accordingly, can be used to treat various acute and chronic inflammatory conditions/disorders such as rheumatoid arthritis.

The pharmaceutical composition of the invention may be prepared by mixing the first active ingredient with the second active ingredient. Therefore, in a further aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a first active ingredient which is a $P2X_7$ receptor antagonist, with a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE).

The first and second active ingredients may alternatively be administered simultaneously (other than in admixture as described above), sequentially or separately to treat inflammatory conditions. By sequential is meant that the first and second active ingredients are administered, in any order, one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The first and second active ingredients are conveniently administered by oral or parenteral administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

Oral administration is preferred.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients employed, the mode of administration, the treatment desired and the condition or disorder indicated. However, in general, satisfactory results will be obtained when the total, combined, daily dosage of first and second active ingredients, when taken orally, is in the range from 10 to 500 milligrammes (mg), particularly from 10, 20, 30, 40 or 50 to 450, preferably to 400, more preferably to 300 mg.

The pharmaceutical composition, pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The present invention further provides the use of a pharmaceutical composition, pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an inflammatory disorder.

Also, the present invention provides a method of treating an inflammatory disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition of the invention to a patient in need thereof.

Still further, the present invention provides a method of treating an inflammatory disorder which comprises simultaneously, sequentially or separately administering:
(a) a (therapeutically effective) dose of a first active ingredient which is a $P2X_7$ receptor antagonist; and
(b) a (therapeutically effective) dose of a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE),
to a patient in need thereof.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The present invention will now be further understood by reference to the following illustrative examples.

Example 1

Pharmacological analysis to determine the effect of TACE inhibitor / $P2X_7$ antagonist combinations (without addition of a $P2X_7$ agonist).

Human peripheral blood from healthy human volunteers was collected in lithium-heparin blood tubes. Test mixtures were added and the blood was incubated at 37 degrees centigrade for 15 - 60 minutes. Test mixtures can compromise of vehicle as control, a $P2X_7$ receptor antagonist, or a combination of a $P2X_7$ receptor antagonist together with a TACE inhibitor. Lipopolysacharide (LPS) was then added to the blood and this was incubated for a further 3 - 6 hours at 37 degrees centigrade. After incubation, samples of cell supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatant, by specific ELISA for cytokines, including IL-1, IL-18, TNFα, IL2, IL6, IL8, and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a $P2X_7$ receptor antagonist alone, or in the

presence of a TACE inhibitor alone, or in the presence of a combination of a $P2X_7$ receptor antagonist with a TACE inhibitor were determined. The effects of the antagonists / inhibitors alone and in combination were then compared. Statistically significant levels of inhibitory activity against a single mediator or on multiple mediators by $P2X_7$ antagonist / TACE inhibitor combinations, in comparison to that achieved by either a $P2X_7$ antagonist or a TACE inhibitor alone, is an indicator for increased efficacy in the treatment of disease.

Example 2

Pharmacological analysis to determine the effect of TACE inhibitor / $P2X_7$ anatagonist combinations (with addition of a $P2X_7$ agonist).

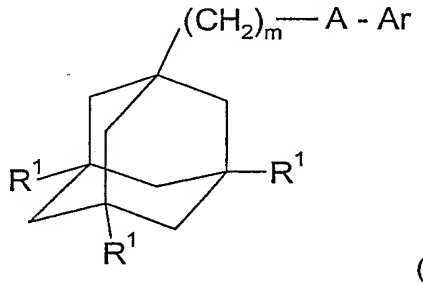
Human peripheral blood from healthy human volunteers was collected in lithium-heparin blood tubes. Test mixtures were added to the blood and incubated at 37 degrees centrigrade for 15 - 60 minutes. Test mixtures can compromise of vehicle as control, a $P2X_7$ receptor antagonist, or a combination of a $P2X_7$ receptor antagonist together with a TACE inhibitor. Lipopolysacharide (LPS) was then added to the blood and this was incubated for a further 3 - 6 hours at 37 degrees centigrade. The $P2X_7$ receptor agonist ATP was added and after incubation for a further 30 minutes at 37 degrees centigrade, samples of blood supernatants were transferred to a 96-well plate for subsequent cytokine and mediator measurements. The formation of inflammatory mediators was measured in the cell supernatant, by specific ELISA for cytokines, including IL-1, IL-18, TNFα, IL2, IL6, IL8, and for other mediators including PGE2, NO and matrix metalloproteinases (MMPs). The levels of mediators released in the presence of a $P2X_7$ receptor antagonist alone, or in the presence of a combination of a $P2X_7$ receptor antagonist with a TACE inhibitor were determined. The effects produced by a $P2X_7$ antagonist alone and in combination with a TACE inhibitor were then compared. Statistically significant levels of inhibitory activity against a single mediator or on multiple mediators by $P2X_7$ antagonist / TACE inhibitor combinations in comparison to that achieved by a $P2X_7$ antagonist alone is an indicator for increased efficacy in the treatment of disease.

CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient which is a $P2X_7$ receptor antagonist, and a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE).

2. A composition according to claim 1, wherein the $P2X_7$ receptor antagonist is an adamantyl derivative.

3. A composition according to claim 1 or claim 2, wherein the $P2X_7$ receptor antagonist is a compound of formula



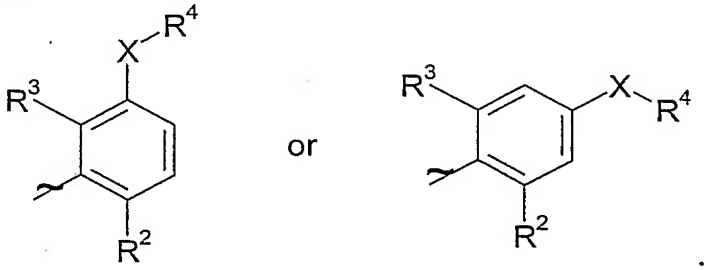
(I)

wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

Ar represents a group



;

X represents a bond, an oxygen atom or a group CO, $(CH_2)_{1-6}$, CH=, $(CH_2)_{1-6}O$, $O(CH_2)_{1-6}$, $O(CH_2)_{2-6}O$, $O(CH_2)_{2-3}O(CH_2)_{1-3}$, CR'(OH), $(CH_2)_{1-3}O(CH_2)_{1-3}$, $(CH_2)_{1-3}O(CH_2)_{2-3}O$, NR^5, $(CH_2)_{1-6}NR^5$, $NR^5(CH_2)_{1-6}$, $(CH_2)_{1-3}NR^5(CH_2)_{1-3}$, $O(CH_2)_{2-6}NR^5$, $O(CH_2)_{2-3}NR^5(CH_2)_{1-3}$, $(CH_2)_{1-3}NR^5(CH_2)_{2-3}O$, $NR^5(CH_2)_{2-6}O$,

$NR^5(CH_2)_{2-3}O(CH_2)_{1-3}$, $CONR^5$, NR^5CO, $S(O)_n$, $S(O)_nCH_2$, $CH_2S(O)_n$, SO_2NR^5 or NR^5SO_2;

n is 0, 1 or 2;

R' represents a hydrogen atom or a C_1-C_6 alkyl group;

one of R^2 and R^3 represents a halogen, cyano, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one C_3-C_6 cycloalkyl, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkyloxy optionally substituted by at least one C_3-C_6 cycloalkyl, and (iv) C_3-C_8 cycloalkyloxy, each of these groups being optionally substituted by one or more fluorine atoms, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

either R^4 represents a 3- to 9-membered saturated or unsaturated aliphatic heterocyclic ring system containing one or two nitrogen atoms and optionally an oxygen atom, the heterocyclic ring system being optionally substituted by one or more substituents independently selected from fluorine atoms, hydroxyl, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$,

or R^4 represents a 3- to 8-membered saturated carbocyclic ring system substituted by one or more substituents independently selected from $-NR^6R^7$, $-(CH_2)_rNR^6R^7$ and $-CONR^6R^7$, the ring system being optionally further substituted by one or more substituents independently selected from fluorine atoms, hydroxyl and C_1-C_6 alkyl;

r is 1, 2, 3, 4, 5 or 6;

R^5 represents a hydrogen atom or a C_1-C_6 alkyl or C_3-C_8 cycloalkyl group;

R^6 and R^7 each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

with the provisos that,

(a) when A represents C(O)NH and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(b) when A represents C(O)NH and X represents a group $(CH_2)_{1-6}$ or $O(CH_2)_{1-6}$, then R^4 does not represent an unsubstituted imidazolyl, unsubstituted morpholinyl, unsubstituted piperidinyl or unsubstituted pyrrolidinyl group, and

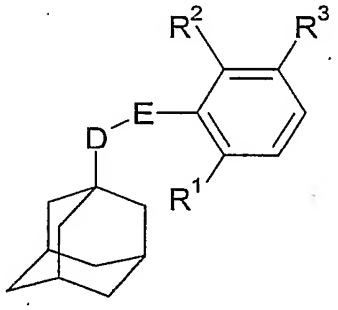
(c) when A represents NHC(O) and R^4 represents an unsubstituted 3- to 8-membered saturated aliphatic heterocyclic ring system containing one nitrogen atom, then X is other than a bond, and

(d) when A represents NHC(O) and X represents $O(CH_2)_{1-6}$, $NH(CH_2)_{1-6}$ or SCH_2, then R^4 does not represent an unsubstituted 1-piperidinyl or unsubstituted 1-pyrrolidinyl group, and

(e) when A represents NHC(O) and X represents $O(CH_2)_{2-3}NH(CH_2)_2$, then R^4 does not represent an imidazolyl group;

or a pharmaceutically acceptable salt or solvate thereof.

4. A composition according to claim 1 or claim 2, wherein the $P2X_7$ receptor antagonist is a compound of formula



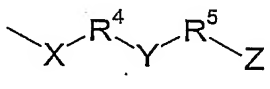
(II)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent a hydrogen or halogen atom, or an amino, nitro, C_1-C_6 alkyl or trifluoromethyl group;

R^3 represents a group of formula



(III);

X represents an oxygen or sulphur atom or a group NH, SO or SO_2;

Y represents an oxygen or sulphur atom or a group NR^{11}, SO or SO_2;

Z represents a group -OH, -SH, $-CO_2H$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6-alkylsulphinyl, C_1-C_6-alkylsulphonyl, $-NR^6R^7$, $-C(O)NR^8R^9$, imidazolyl, 1-methylimidazolyl, $-N(R^{10})C(O)$-C_1-C_6 alkyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, $-OC(O)NR^{12}R^{13}$, $-OCH_2OC(O)R^{14}$, $-OCH_2OC(O)OR^{15}$ or $-OC(O)OCH_2OR^{16}$;

R^4 represents a C_2-C_6 alkyl group;

R^5 represents a C_1-C_6 alkyl group;

R^6, R^7, R^8, R^9, R^{10}, R^{12} and R^{13} each independently represent a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one hydroxyl group;

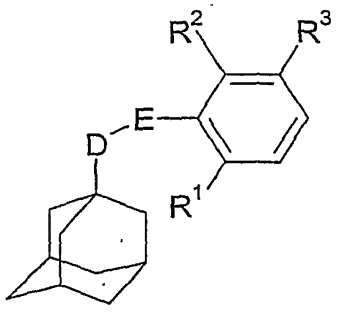
R^{11} represents a hydrogen atom, or a C_1-C_6 alkyl group optionally substituted by at least one substituent independently selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15} and R^{16} each independently represent a C_1-C_6 alkyl group;

with the provisos that (i) when E represents NHC(O), X represents O, S or NH and Y represents O, then Z represents $-NR^6R^7$ where R^6 represents a hydrogen atom and R^7 represents either a hydrogen atom or a C_1-C_6 alkyl group substituted by at least one hydroxyl group, and (ii) when E represents NHC(O), X represents O, S or NH, Y represents NH and R^5 represents CH_2CH_2, then Z is not -OH or imidazolyl;

or a pharmaceutically acceptable salt or solvate thereof.

5. A composition according to claim 1 or claim 2, wherein the $P2X_7$ receptor antagonist is discloses a compound of formula



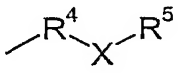
(IV)

wherein D represents CH_2 or CH_2CH_2;

E represents C(O)NH or NHC(O);

R^1 and R^2 each independently represent hydrogen, halogen, amino, nitro, C_1-C_6 alkyl or trifluoromethyl, but R^1 and R^2 may not both simultaneously represent hydrogen;

R^3 represents a group of formula

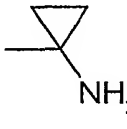


(V);

R^4 represents a C_1-C_6 alkyl group;

X represents an oxygen or sulphur atom or a group NR^{13}, SO or SO_2;

R^5 represents hydrogen, or R^5 represents C_1-C_6 alkyl or C_2-C_6 alkenyl, each of which may be optionally substituted by at least one substituent selected from halogen, hydroxyl, (di)-C_1-C_6-alkylamino, -Y-R^6,



, and

a 5- or 6-membered heteroaromatic ring comprising from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulphur which heteroaromatic ring may itself be optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1-C_6 alkyl;

Y represents an oxygen or sulphur atom or a group NH, SO or SO_2;

R^6 represents a group -R^7Z where R^7 represents a C_2-C_6 alkyl group and Z represents an -OH, $-CO_2H$, $-NR^8R^9$, $-C(O)NR^{10}R^{11}$ or $-N(R^{12})C(O)$-C_1-C_6 alkyl group, and, in the case where Y represents an oxygen or sulphur atom or a group NH, R^6 additionally represents hydrogen, C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, $-C(O)NR^{14}R^{15}$, $-CH_2OC(O)R^{16}$, $-CH_2OC(O)OR^{17}$ or $-C(O)OCH_2OR^{18}$;

R^8, R^9, R^{10}, R^{11} and R^{12} each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

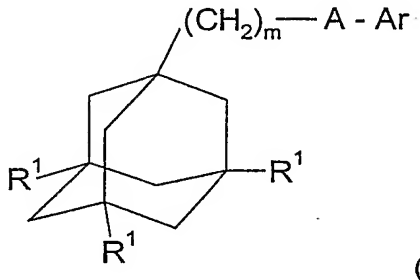
R^{13} represents hydrogen, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylmethyl, or R^{13} represents a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from hydroxyl and C_1-C_6 alkoxy; and

R^{14}, R^{15}, R^{16}, R^{17} and R^{18} each independently represent a C_1-C_6 alkyl group;

with the proviso that when E is C(O)NH, X is O, NH or N(C_1-C_6 alkyl), then R^5 is other than a hydrogen atom or an unsubstituted C_1-C_6 alkyl group;

or a pharmaceutically acceptable salt or solvate thereof.

6. A composition according to claim 1 or claim 2, wherein the $P2X_7$ receptor antagonist is a compound of formula



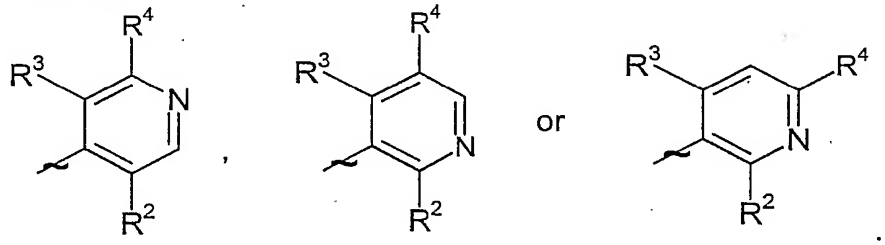
(VI)

wherein m represents 1, 2 or 3;

each R^1 independently represents a hydrogen or halogen atom;

A represents C(O)NH or NHC(O);

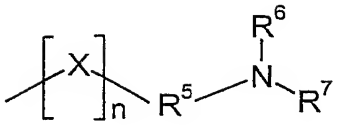
Ar represents a group



;

one of R^2 and R^3 represents halogen, nitro, amino, hydroxyl, or a group selected from (i) C_1-C_6 alkyl optionally substituted by at least one halogen atom, (ii) C_3-C_8 cycloalkyl, (iii) C_1-C_6 alkoxy optionally substituted by at least one halogen atom, and (iv) C_3-C_8 cycloalkyloxy, and the other of R^2 and R^3 represents a hydrogen or halogen atom;

R^4 represents a group



(X);

X represents an oxygen or sulphur atom or a group >N-R^8;

n is 0 or 1;

R^5 represents a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

R^6 and R^7 each independently represent a hydrogen atom, C_1-C_6 alkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen, C_1-C_6 alkoxy, and (di)-C_1-C_4 alkylamino (itself optionally substituted by at least one hydroxyl group)), or C_3-C_8 cycloalkyl (optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy); and

R^8 represents a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

with the provisos that:

(a) when n is 0, then A is NHC(O), and

(b) when n is 1, X represents oxygen and A is C(O)NH, then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl; and

(c) when n is 1, X is oxygen, sulphur or >NH and A is NHC(O), then R^6 and R^7 do not both simultaneously represent a hydrogen atom or do not both simultaneously represent an unsubstituted C_1-C_6 alkyl, or when one of R^6 and R^7 represents a hydrogen atom, then the other of R^6 and R^7 does not represent an unsubstituted C_1-C_6 alkyl or $-CH_2CH_2OH$;

or a pharmaceutically acceptable salt or solvate thereof.

7. A composition according to claim 1 or claim 2, wherein the $P2X_7$ receptor antagonist is:

2-Chloro-5-[[2-(2-hydroxy-ethylamino)-ethylamino]-methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide, dihydrochloride,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

(R)-2-Chloro-5-[3-[(2-hydroxy-1-methylethyl)amino]propyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[(2-hydroxyethyl)amino]ethoxy]methyl]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[3-(methylamino)propoxy]propyl]-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)benzamide,

2-Chloro-5-[3-(3-hydroxy-propylamino)-propoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylamino)ethylamino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-(3-hydroxypropylsulfonyl)ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[2-[2-[(2-hydroxyethyl)amino]ethoxy]ethoxy]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[[2-[[2-(1-methyl-1*H*-imidazol-4-yl)ethyl]amino]ethyl]amino]-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-piperazin-1-ylmethyl-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(4-piperidinyloxy)-*N*-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

2-Chloro-5-(2,5-diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide,

2-Chloro-5-[3-[(3-hydroxypropyl)amino]propyl]-N-(tricyclo[3.3.1.1]dec-1-ylmethyl)-benzamide hydrochloride,

2-Chloro-5-(piperidin-4-ylsulfinyl)-N-(tricyclo[3.3.1.1^{3,7}]dec-1-ylmethyl)-benzamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(3-hydroxypropyl)amino]propyl}-isonicotinamide dihydrochloride,

N-(1-Adamantylmethyl)-2-chloro-5-(3-{[(1*R*)-2-hydroxy-1-methylethyl]amino}propyl)nicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-[3-(ethylamino)propyl]isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-{3-[(2-hydroxyethyl)amino]propyl}-isonicotinamide,

N-(1-Adamantylmethyl)-5-chloro-2-(3-{[(2*S*)-2-hydroxypropyl]amino}propyl)isonicotinamide,

or a pharmaceutically acceptable salt or solvate of any one thereof.

8. A composition according to any one of claims 1 to 7, wherein the inhibitor of proTNFα convertase enzyme is:

3-Amino-N-hydroxy-α-(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide,

2(S), 3(S)-Piperidinedicarboxamide, N3-hydroxy-1-methyl-N2-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl],

3-Thiomorpholinecarboxamide, 4-[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl,

5-Hexenoic acid, 3-[(hydroxyamino)carbonyl]-2-(2-methylpropyl)-6-phenyl-, 2-(2-methylpropyl)-2-(methylsulfonyl)hydrazide, (2R,3S,5E),

2-Piperidinecarboxamide, N,5-dihydroxy-1-[[4-(1-naphthalenylmethoxy)phenyl]sulfonyl]-, (2R,5R),

Pentanamide, 3-(formylhydroxyamino)-4-methyl-2-(2-methylpropyl)-N-[(1S,2S)-2-methyl-1-[(2-pyridinylamino)carbonyl]butyl]-, (2R,3S),

2-Propenamide, N-hydroxy-3-[3-[[(4-methoxyphenyl)sulfonyl](1-methylethyl)amino]phenyl]-3-(3-pyridinyl)-, (2E),

Benzamide, N-(2,4-dioxo-1,3,7-triazaspiro[4.4]non-9-yl)-4-[(2-methyl-4-quinolinyl)methoxy],

Benzamide, N-[(1-acetyl-4-piperidinyl)(2,5-dioxo-4-imidazolidinyl)methyl]-4-[(2-methyl-4-quinolinyl)methoxy], or

2,4-Imidazolidinedione, 5-methyl-5-[[[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]methyl].

9. A composition according to any one of claims 1 to 8 which is formulated for oral administration.

10. A process for the preparation of a pharmaceutical composition as defined in any one of claims 1 to 8 which comprises mixing the first active ingredient with the second active ingredient.

11. Use of a composition according to any one of claims 1 to 8 in the manufacture of a medicament for the treatment of an inflammatory disorder.

12. Use according to claim 11, wherein the inflammatory disorder is rheumatoid arthritis.

13. A method of treating an inflammatory disorder which comprises administering a therapeutically effective amount of a pharmaceutical composition as defined in any one of claims 1 to 8 to a patient in need thereof.

14. A method according to claim 13, wherein the inflammatory disorder is rheumatoid arthritis.

15. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, and a preparation of a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE), for simultaneous, sequential or separate use in therapy.

16. A kit comprising a preparation of a first active ingredient which is a $P2X_7$ receptor antagonist, a preparation of a second active ingredient which is an inhibitor of proTNFα convertase enzyme (TACE), and instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000196

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/166, A61K 31/167, A61K 31/47, A61P 29/02, C07C 235/46
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61P, C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, MEDLINE, EMBASE, EPODOC, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 44170 01 (ASTRAZENECA AB), 21 June 2001 (21.06.2001) --	1-16
Y	WO 0142194 A1 (ASTRAZENECA AB), 14 June 2001 (14.06.2001) --	1-16
Y	WO 0061569 A1 (ASTRAZENECA AB), 19 October 2000 (19.10.2000) --	1-16
Y	WO 02096426 A1 (BRISTOL-MYERS SQUIBB COMPANY), 5 December 2002 (05.12.2002) --	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2004	07 -05- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Erika Stenroos/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000196

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-14
because they relate to subject matter not required to be searched by this Authority, namely:

see next page

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000196

Claims 13-14 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body (PCT/Rule. 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000196

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9918074 A1 (DU PONT PHARMACEUTICALS COMPANY), 15 April 1999 (15.04.1999) -- --------	1-16

WO	44170	01	21/06/2001	NONE			
WO	0142194	A1	14/06/2001	AU	2036301	A	18/06/2001
				BR	0016227	A	01/10/2002
				CA	2394236	A	14/06/2001
				CN	1407968	T	02/04/2003
				CZ	20021982	A	15/01/2003
				EE	200200295	A	15/08/2003
				EP	1240132	A	18/09/2002
				HU	0300618	A	28/07/2003
				IL	149762	D	00/00/0000
				JP	2003516382	T	13/05/2003
				NO	20022727	A	29/07/2002
				SE	9904505	D	00/00/0000
				SK	7622002	A	09/01/2003
				US	2002193414	A	19/12/2002

WO	0061569	A1	19/10/2000	AU	3994700	A	14/11/2000
				AU	5547000	A	02/01/2001
				BR	0009651	A	08/01/2002
				CA	2368829	A	19/10/2000
				CN	1353702	T	12/06/2002
				CZ	20013608	A	15/05/2002
				EE	200100525	A	16/12/2002
				EP	1171432	A	16/01/2002
				GB	0002330	D	00/00/0000
				HU	0202214	A	28/10/2002
				IL	145505	D	00/00/0000
				JP	2002541249	T	03/12/2002
				NO	20014894	A	10/12/2001
				NZ	514477	A	29/04/2003
				PL	350907	A	10/02/2003
				SK	13422001	A	09/05/2002
				TR	200102911	T	00/00/0000
				US	6492355	B	10/12/2002
				AP	200102041	D	00/00/0000
				AT	250036	T	15/10/2003
				AU	751103	B	08/08/2002
				AU	4950499	A	07/02/2000
				BR	9912109	A	02/05/2001
				CA	2336968	A	27/01/2000
				DE	69911415	D	00/00/0000
				DK	1095021	T	24/11/2003
				EE	200100010	A	17/06/2002
				EP	1095021	A,B	02/05/2001
				SE	1095021	T3	
				HR	20010039	A	31/12/2001
				HU	0103224	A	28/01/2002
				IL	140346	D	00/00/0000
				JP	2002520395	T	09/07/2002
				NO	20010211	A	15/03/2001
				NZ	508923	A	27/09/2002
				PL	345388	A	17/12/2001
				SE	9901270	D	00/00/0000
				ZA	200108265	A	08/01/2003
WO	02096426	A1	05/12/2002	CA	2447475	A	05/12/2002
				EP	1397137	A	17/03/2004
				US	2003130273	A	10/07/2003

WO	9918074	A1	15/04/1999	AU	747239	B	09/05/2002
				AU	9686698	A	27/04/1999
				BR	9815398	A	31/10/2000
				CA	2305679	A	15/04/1999
				CN	1272841	T	08/11/2000
				EE	200000199	A	16/04/2001
				EP	1027332	A	16/08/2000
				HR	980533	A	31/10/1999
				HU	0100186	A	28/05/2001
				IL	135289	D	00/00/0000
				JP	2001519331	T	23/10/2001
				NO	315648	B	06/10/2003
				NO	20000783	A	29/05/2000
				NZ	504088	A	28/09/2001
				PL	339738	A	02/01/2001
				SK	4462000	A	04/06/2002
				TW	541304	B	00/00/0000
				US	6057336	A	02/05/2000
				US	6610731	B	26/08/2003
				US	2003134827	A	17/07/2003
				ZA	9808967	A	03/04/2000